Cardiovascular Effects of Methoxyflurane
Anesthesia in Man

Joe A. Walker, M.D., G. W. N. Eggers, Jr., M.D., Charles R. Allen, M.D., Ph.D.

Preliminary clinical experience has shown methoxyflurane to have significant properties which warrant its use to continue. Review of our anesthesia records, however, indicated that patients anesthetized with this agent developed consistently both a decrease in systolic blood pressure and an increase in heart rate of about 20 per cent. The physiological effects of these methoxyflurane anesthetizations were complicated by a high incidence of patients with cardiovascular disease and other clinical variables as premedication, surgical manipulation and surgical positioning. This report is a study of the cardiovascular effects of methoxyflurane in patients under controlled conditions. Our findings have been compared with those from a similar study in which halothane was the anesthetic agent.

Method

Five adult male subjects scheduled for elective surgical procedures and without demonstrable cardiovascular disease were studied. All subjects were evaluated while in the supine position, in the fasting state, without premedication, and prior to operation. Procaine hydrochloride, 1 per cent, was utilized to anesthetize skin puncture sites. A Cournand needle (18 gauge) was inserted into either a brachial or radial artery for pressure measurements and blood sampling. Electrocardiograph electrodes were attached and the tracing monitored on a cathode ray oscilloscope. A sterile polyethylene catheter (36 inches long, 1 mm. outside diameter) was inserted via a 16 gauge needle into a median antecubital vein, the catheter attached to a strain gauge transducer and the pressure tracing monitored on the oscilloscope. The catheter was inserted until its tip entered the thorax (indicated by an immediate pressure response to coughing) and then gradually advanced until right ventricular or pulmonary artery pressures were observed.

The cardiac rhythm was monitored throughout the period of advancement of the catheter. Although serious arrhythmias were not observed, premature ventricular contractions occasionally did occur. The catheter was allowed to remain in the right ventricle only a few seconds and then was withdrawn until right atrial pressures were obtained. The catheter was then withdrawn another 5 cm. and affixed to the arm to prevent migration. The 16 gauge needle was removed, sliding back over the catheter where it remained until the procedure was completed.

Cardiac output determinations were performed by the central injection of predetermined volumes of indocyanine green dye.¹ The concentration of the dye in the arterial blood was measured with a Gilford Cuvette Densitometer (Model 103-B) attached to a constant flow system (Gilford Model 105-S), and the resultant curve recorded on a Texas Instruments rectilinear recorder. The cardiac output was calculated by the method of Stewart and Hamilton.² ³ Just prior to each output determination, arterial systolic, diastolic and electrically integrated mean pressures were recorded on a Gilson direct writing recorder. Systemic vascular resistance was calculated from the formula: resistance = mean arterial pressure (mm. of mercury) × 60 × 1.332/cardiac output (liters/minute).⁴ Electrocardiographic tracings were made throughout each cardiac output determination in order to record the heart rate. Immediately following the output determination, arterial blood samples for pH, hematocrit value, oxygen and carbon dioxide content and oxygen capacity were obtained. Arterial pH determinations were measured at 37° C. with a Beckman Zeromatic pH meter (Model 7B) within five minutes of sampling. Hematocrit determinations were measured with Wintrobe tubes. Oxygen and carbon dioxide

Accepted for publication May 14, 1962. Drs. Walker and Allen are in the Department of Anesthesiology, University of Texas Medical Branch, Galveston, Texas. Dr. Egger's present address: University of Missouri School of Medicine, Columbia, Missouri.
Table 1. Average Physical Values for the
Subjects in Each Group Studied

<table>
<thead>
<tr>
<th></th>
<th>Methoxyflurane (Value ± S. D.)</th>
<th>Halothane (Value ± S. D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>51 ± 13</td>
<td>31 ± 8</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.78 ± 0.07</td>
<td>1.93 ± 0.27</td>
</tr>
<tr>
<td>Whole blood oxygen capacity (%)</td>
<td>19.72 ± 0.62</td>
<td>19.76 ± 1.37</td>
</tr>
</tbody>
</table>

S. D.—Standard Deviation.

content and oxygen capacity of arterial blood were determined using the manometric method of Van Slyke and Neill. The arterial Pco₂ was obtained from the Singer-Hastings nomogram.

After the patient had assumed a resting state with the pulse rate, blood pressure and respiration stable, a cardiac output determination was made prior to the institution of anesthesia. Each subject was then given a 'sleep' dose of thiopental (150-200 mg.) intravenously followed by methoxyflurane vaporized with oxygen at a flow rate of 2 to 4 liters per minute. A Foregger 'copper kettle' vaporizer was utilized to administer the methoxyflurane and a to-and-fro absorption, semiclosed technique was employed. After approximately ten minutes of methoxyflurane administration, 20 mg. of succinylcholine was given intravenously. The larynx was exposed and sprayed with 6 per cent cocaine and auffed endotracheal tube inserted. Anesthetic depth was increased until a moderate plane of surgical anesthesia was achieved. The anesthetic state was allowed to stabilize for at least 35 minutes before the second cardiac output determination was done. The respirations were spontaneous and unassisted throughout except for the period of intubation and immediately thereafter.

For comparison, we include data from another investigation in which halothane was administered to ten healthy volunteers. These subjects were studied in identically the same manner except the stabilized anesthetic state was achieved in the latter group by the inhalation of 1.5 per cent halothane in oxygen delivered through a Fluotec vaporizer.

Electroencephalograms were made during the period of anesthesia. Established criteria for electroencephalographic levels of anesthesia with halothane were utilized for determination of depth of anesthesia with either halothane or methoxyflurane. The use of this criteria for establishing anesthetic levels with methoxyflurane is supported by the report of Artuso et al.

Results

Table 1 compares the average physical values of the subjects studied in the methoxyflurane and halothane groups. The average age of the methoxyflurane group was higher and represented the only significant difference in values between the two groups.

Table 2 records the arterial blood determinations for each group prior to and during the period of anesthesia. All values are similar and are those expected to occur when respirations are spontaneous and unassisted during inhalation anesthesia. The only significant differences between the two groups were the changes in the hematocrit values.

The electroencephalograms recorded during the study revealed the depth of anesthesia for both groups to be comparable. All anesthetized subjects were at electroencephalographic levels 2 or 3 at the time when cardiac index determinations were made. Muscle relaxation was judged to be more profound with methoxyflurane than with halothane at similar electroencephalographic levels of anesthesia.

Table 3 compares the cardiovascular effects of both methoxyflurane and halothane. There was no significant difference between the control values of the two groups. Both drugs produced decreases in cardiac index, mean arterial pressure and systemic vascular resistance. The heart rate increased an average of 7 beats/minute during methoxyflurane anesthesia which was significantly different (P < .01) when compared to the heart rate during halothane anesthesia. As a result of the difference in heart rate, the stroke volume/m² was significantly less (P < .05) during methoxyflurane anesthesia. There were no other statistically significant differences in the cardiovascular responses to these two agents.

Discussion

Factors influencing cardiac index in man include fear, apprehension, exercise, body position, blood volume, pain, arterio-venous shunts
and temperature. The subjects included in this report were healthy, quiescent, comfortable and in the supine reflex position. Partial evidence that the methoxyflurane subjects were not apprehensive was the increase in heart rate during anesthesia. The values for control cardiac indices (2.75 and 2.65 liters/minute/m²) in both groups indicate that the subjects were comfortable and free of apprehension for these values are in the normal range when compared to data previously obtained with this technique. The validity of the method has been confirmed with simultaneous Fick determinations for cardiac index and the basal state has been confirmed with simultaneous oxygen consumption studies. In normal healthy, quiescent, supine subjects, either awake or anesthetized, the paramount factors capable of causing a decrease in cardiac index are extremes in heart rate, decreased myocardial contractility and decreased venous return to the heart. The decrease in cardiac index during methoxyflurane anesthesia was not due to an extreme change in heart rate. Although myocardial contractility was not measured, a decrease in contractility due to the direct effects of methoxyflurane on the myocardium is the most probable explanation. A decreased venous return to the heart may have been present also since mean arterial pressure and peripheral resistance decreased (table 3). There was no direct evidence to establish clearly the cause of the decreased cardiac index measured during methoxyflurane anesthesia.

The hypotension associated with methoxyflurane was primarily due to a decrease in cardiac output (table 3). Halothane has been reported to produce hypotension primarily due to depression of the myocardium and a resultant decreased cardiac output. In contrast, the hypotension following the administration of halothane in our study was primarily due to a decrease in systemic vascular resist-

---

### Table 2. Average Arterial Blood Determinations for Each Group Studied

<table>
<thead>
<tr>
<th></th>
<th>Methoxyflurane</th>
<th>Halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.04</td>
<td>7.36 ± 0.07</td>
</tr>
<tr>
<td>Carbon dioxide content (mM/L)</td>
<td>20.8 ± 1.8</td>
<td>22.2 ± 2.1</td>
</tr>
<tr>
<td>PCO₂ (mm Hg)</td>
<td>39 ± 3</td>
<td>47 ± 7</td>
</tr>
<tr>
<td>Oxygen content (%)</td>
<td>18.49 ± 0.75</td>
<td>19.09 ± 0.49</td>
</tr>
<tr>
<td>Saturation of hemoglobin (%)</td>
<td>95.3 ± 2.3</td>
<td>100.00±4.8</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>45 ± 4</td>
<td>47 ± 3</td>
</tr>
</tbody>
</table>

S. D.—Standard Deviation.
* Unassisted, spontaneous ventilation.
† Superscript refers to ml./O₂/100 ml. blood in excess of that required to saturate hemoglobin (i.e., physically dissolved O₂).

---

### Table 3. Cardiovascular Effects of Methoxyflurane and Halothane

<table>
<thead>
<tr>
<th></th>
<th>Methoxyflurane</th>
<th>Halothane</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.75 ± 0.35</td>
<td>-0.27</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>83.4 ± 17.0</td>
<td>-17.0</td>
</tr>
<tr>
<td>Heart rate (Beats/minute)</td>
<td>74 ± 11</td>
<td>+7</td>
</tr>
<tr>
<td>Systemic vascular resistance (Dynes·Sec·cm⁻²)</td>
<td>1,356 ± 188</td>
<td>-147</td>
</tr>
<tr>
<td>Stroke volume/m² (ml./beat/m²)</td>
<td>38 ± 7</td>
<td>-6</td>
</tr>
</tbody>
</table>

S. D.—Standard Deviation.
* Average difference between control and anesthetized state. † Indicates an increase, †† indicates a decrease.
ance (table 3). This is in agreement with other observers and does not deny the myocardial depressant property of halothane, particularly with overdosage.

The 'light' level of anesthesia, the absence of other depressant drugs (e.g., premedicants, nitrous oxide) and spontaneous respiration with associated hypercarbia undoubtedly contributed to the cardiovascular effects of both methoxyflurane and halothane included in this report. Since both groups were equally effects, their comparison appears justified.

Methoxyflurane, a halogenated ether, was anticipated to provide properties similar to diethyl ether without flammability. Although conflicting reports are in the literature, many observers consider that the administration of diethyl ether results in increases of cardiac output and rate, with normal or elevated systemic arterial pressure during 'light' anesthesia. The hemodynamic effects of methoxyflurane simulate those of diethyl ether only in regard to heart rate. Clinical experience with approximately 1,000 cases of methoxyflurane has shown cardiovascular changes similar to those produced with halothane. The results of this study support our clinical experience.

Summary

'Light' methoxyflurane-oxygen anesthesia in unpremedicated, healthy subjects resulted in a decreased cardiac index, decreased mean arterial pressure, decreased systemic vascular resistance, increased heart rate and decreased stroke volume/m. The cardiovascular effects of methoxyflurane anesthesia resemble those of halothane anesthesia rather than the effects reported with diethyl ether. The significant differences between halothane and methoxyflurane anesthesia were an increase in heart rate and a decrease in stroke volume with the latter agent.

The hypotension observed during methoxyflurane anesthesia was primarily due to a decrease in cardiac index.

References